REMARKS

Claims 1, 26, 28, and 53 are pending in the present application.

Claims 2-25, 27, and 29-52 have been canceled without prejudice.

Claim 1 has been amended to correct inadvertent editorial errors. No new matter is added by this amendment.

Prior Rejections.

Applicants gratefully acknowledge that the prior rejections have been withdrawn.

Rejections Under 35 U.S.C. §103(a).

Claim 1 stands rejected under 35 U.S.C. §103(a) as allegedly being obvious over the combination of Haupt *et al.* in view of Gordan *et al.*, Andersen *et al.*, Luther *et al.*, Lu *et al.*, Xiang *et al.*, and Dueger *et al.* Claim 26 stands rejected over the same references as claim 1 and further in view of Bennet *et al.* Claim 28 stands rejected over the same references as claim 1 and further in view of Tanabe *et al.* Claim 53 stands rejected over the same references as claim 1 and further in view of Bennett *et al.* and Tanabe *et al.* These rejections are unwarranted.

To establish a *prima facie* case of obviousness, the Patent and Trademark Office bears the burden of satisfying three requirements. First, as the U.S. Supreme Court recently held in *KSR International Co. v. Teleflex Inc.* 82 USPQ2d 1385 (2007):

> [A] court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions. ...it [may] be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. ...it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does... because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." *Id.* at 1396.

Secondly, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ 1016, 1023 (C.C.P.A. 1970). Thirdly, all words in a claim must be considered in judging the patentability of that claim against the prior art. *In re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970). In addition, a reference should be considered for all that it would have fairly suggested to those of ordinary skill in the art, not just those parts that would support a conclusion of obviousness (see e.g., *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 230 USPQ 416 (Fed. Cir. 1986)).

In *KSR* the U.S. Supreme Court endorsed the four *Graham* factual inquiries listed below when seeking to determine obviousness. *KSR*, 82 USPQ2d at 1391. The four factual inquiries that must be addressed are as follows: (1) determining the scope and contents of the prior art; (2) ascertaining the differences between the prior art and the claims under consideration; (3) resolving the level of ordinary skill in the pertinent art or technological areas; and (4) evaluating evidence of secondary considerations. *Graham v. John Deere*, 383 U.S. at 17, 148 USPQ at 467. The *Graham* factual inquiries of Items (1) and (2) and their applicability are explained below.

Scope and content of the prior art.

Haupt *et al.* provide a review of potential strategies for DNA vaccination against tumor-associated antigens for anti-tumor therapy. This reference discusses a number of advantages and difficulties associated with DNA vaccination against tumor-associated antigens. In particular, this reference points out that all tumor antigens being expressed tissue specifically could be possible targets for DNA vaccines if the expressing tissue is not essential for health and survival (p. 233, col. 1). Peyer's patches, however, play a vital role in the immune response against microorganisms and are essential to health and survival. Thus, this reference teaches that the results of targeting a given tumor-associated antigen are limited to specific types of tissues and based on the teaching away in Haupt *et al.* it would not have been obvious to introduce the DNA vaccine orally to specifically target Peyer's patches in the gut. Furthermore, the example referred to by the Examiner (Current Action p. 7) does not address any malignant tumor of epithelial origin as suggested by the Examiner, but specifically to medullary thyroid carcinomas as expressing

calcitonin. There is no reasonable expectation that a process that shows a certain result against medullary thyroid carcinoma would have a similar effect against a tumor in the lower intestines. Lastly, at page 229, col. 1 through page 230, col. 2 the reference discloses a number of methods for delivering a DNA vaccine (e.g., intravenous, intramuscular, and aerosol). Significantly, none of those methods involves oral delivery, much less oral delivery in an attenuated *S. typhimurium* vector as claimed.

Gordan *et al.* disclose that survivin is a good candidate for a universal TAA, some of the qualities needed by an ideal universal TAA have been identified in survivin. There is the possibility of survivin expression in normal tissues (p. 322, col. 2). Although survivin was identified as a strong candidate, it is not a foregone conclusion that it would be a successful target for DNA vaccination. Gordan *et al.* expressly states there is no basis for predicting survivin will be a functional tumor rejection antigen (p. 323, col. 2).

Anderson *et al.* disclose that spontaneous cytotoxic T lymphocyte (CTL) responses against survivin-derived MHC-class I-restricted T cell epitopes have been observed in cancer patients, and posit that survivin may be a useful target for anti-cancer immunotherapy.

Luther *et al.* report that CCL21 expression can induce infiltration of lymphocytes and dendritic cells into secondary lymphoid organs.

Lu *et al.* teaches the use of an attenuated *Salmonella typhimurium* vector for oral delivery of antigens. None of the other applied references teaches or even suggests use of oral delivery or the use of *S. typhimurium*.

Xiang *et al.* discloses use of an oral CEA-based DNA vaccine delivered via live attenuated AroA$^-$ strain of *Salmonella typhimurium*. The efficacy of this vaccine, however, is markedly increased by boosts with a recombinant antibody-IL2 fusion protein.

Dueger *et al.* teaches dam$^-$ *Salmonella* immunization as effective against other *Salmonella* strains, murine typhoid fever, and suggests protection against other proteobacteria pathogens. There is no suggestion of treatment or prevention of cancer.

The Bennett *et al.* and Tanabe *et al.* references disclose the specific sequences of the survivin protein and CCL21.

Differences between the prior art and the claims.

Claim 1 relates to an oral DNA vaccine suitable for eliciting an immune response against cancer cells in a patient comprising a DNA construct operably encoding at least one survivin protein and one CCL21 cytokine in a pharmaceutically acceptable carrier; wherein the DNA construct is incorporated in an attenuated *Salmonella typhimurium* vector that targets Peyer's patches in the gut, and wherein the DNA vaccine induces a cytotoxic T-lymphocyte immune response against tumor cells when orally administered to the patient. While each element of claim 1 may be individually found in the prior art, it is the specific combination of these elements that is claimed, not the individual elements. The present rejection again impermissibly resorts to a *de novo* reconstruction of the claimed invention from isolated teachings of the prior art using the specification as a guide. There is no road-map in the combined teachings of the applied references that would have led one of ordinary skill in the art to prepare the claimed oral DNA vaccine, absent prior knowledge of the present claims. The only evident motivation to combine the specific elements of the present claims is in the application itself. Hindsight use of the teachings of the application as a guide for combining all of the elements of the claims clearly is improper. *In re Fine*, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988). Thus, the rejections at most amount to nothing more than an assertion that it would have been "obvious to try" the claimed combination in view of the isolated prior art teachings of the various elements of the claims. For reasons discussed in detail hereinbelow, that is not a proper basis for a rejection in this case.

The primary reference, Haupt *et al.*, teaches that vaccination against tumor-associated antigens is unpredictable. Therefore, it would not have been predictable to change both the method of administration to oral vaccination and to target specific tissue in the gut, and expect a similar result. A reference must be considered for all that it teaches, not just that which might support a finding of obviousness. The present Office Action does not follow this admonition. The Office Action fails to explain why one of ordinary skill in the art would have ignored the teachings of Haupt *et al.* regarding the inadvisability of targeting tissue specific antigens in essential tissues, while following other portions of the reference.

The present invention does not represent a *predictable* variation of known

elements or techniques in prior fields of endeavor. For *prima facie* obviousness, there must be a reasonable expectation of success that the proposed combination will work. This presupposes that the skilled person is capable of rationally predicting, on the basis of existing knowledge, the successful conclusion of the subject invention without undue experimentation. The more unexplored a technical field of research is, however, the more difficult it is to make predictions about the likelihood of success. Haupt *et al.* clearly indicate that such predictions would not have been possible in the field of vaccines against tumor-associated antigens at the time of the invention due to the unpredictability of overcoming self-tolerance, the heterogeneity of tumor antigen presentation, and the inadvisability of targeting essential tissues.

In addition, the Haupt *et al.* reference mentions several methods for delivering DNA vaccines, including intravenous, intramuscular and aerosol delivery. Haupt *et al.*, however, does not teach or even suggest oral delivery. The Office Action does not provide any articulated reason or rationale as to what would have motivated one of ordinary skill in the art to select the oral *S. typhimurium* vector of Lu *et al.* to deliver the DNA vaccine of the present claims, especially when the primary and other secondary references do not even suggest the use of oral delivery. The applied references do nothing more than disclose isolated elements of the present claims without providing any reason or motivation for one of ordinary skill in the art to have combined the disparate teachings of the references without having prior knowledge of the present application or inventive insight.

The Office Action emphasizes that survivin is one of only four alleged "universal" tumor-associated antigens, implying a finite number of choices. Haupt *et al.*, on the other hand, highlight the unpredictable nature of vaccines targeting tumor-associated antigens, and point to strategies other than targeting "universal" antigens. Thus, the number of potential targets available to one of ordinary skill in the art at the time of the invention was much larger than just four. In addition, Haupt *et al.* selects the four "universal" alleged universal tumor-associated antigens as the best potential candidates while acknowledging there is much testing to be done and that not all of the ideal characteristics of a universal tumor-associated antigen are present. In the present case, there are, in fact, a very large number of potential combinations for the tumor antigen,

the cytokine adjuvant, and the delivery vehicle from which one of ordinary skill would have had to select the claimed combination. The selection of all of these variants based on the applied art clearly would have involved undue experimentation. See also *Takeda Chemical Industries Ltd. v. Alphapharm Pty. Ltd.*, 83 USPQ2d 1169 (Fed. Cir. 2007) (no identification of a predictable solution where prior art discloses a broad selection of compounds).

Conclusion.

As noted above, the prior art does not provide a predictable road-map to combine all of the elements of the present claims together to achieve the required CTL response without undue experimentation, prior knowledge of the present application, or inventive insight. The only road-map to the presently claimed invention of record here is the present application, itself. The "obvious to try" standard upon which the Examiner appears to be relying to combine the disparate elements from the prior art is not applicable to the present claims, however, since the number of alternatives in the case of anti-tumor vaccines (choice of potential antigens, number of antigens to target, combined with choice of cytokine and choice of vector) would have been very large, and the results would not have been predictable (see *KSR*, 82 USPQ2d at 1397). Accordingly, withdrawal of the present obviousness rejections is warranted.

In view of the foregoing, Applicants request reconsideration, allowance of the present claims, and early passage of the application to issue.

Respectfully submitted,

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Talivaldis Cepuritis (Reg. No. 20,818)

OLSON & CEPURITIS, LTD.
20 North Wacker Drive
36th Floor
Chicago, Illinois 60606
(312) 580-1180